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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,855	10/13/2000	Chaitan Khosla	286002021100	6952

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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	9

DATE MAILED: 04/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,855	KHOSLA ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- Th MAILING DATE of this communication app ars on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,24-29 and 42-52* is/are pending in the application.

4a) Of the above claim(s) *44-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,24-29,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the written restriction requirement (Paper No. 6 mailed on January 24, 2002), Applicants filed an election with a preliminary amendment A (Paper No. 7 on March 6, 2002) and a preliminary amendment B (Paper No. 8 on April 3, 2002) adding new claims 44-52. Preliminary amendment A cancelled Claims 10-23 and 30-41. The restriction is reiterated below to include the new claims (in italics). Claims in Groups II-V have been canceled, but are reiterated for completeness.

Restriction

2. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-9, 24-29, and 42-43, drawn to host cells modified to produce polyketides, classified in class 435, subclass 252.3.

II. Claims 10, 13-23, and 30-32, drawn to methods of making polyketides, classified in class 435, subclass 76.

III. Claims 11-12, drawn to methods of assessing genetic modifications in host cells, classified in class 435, subclass 4.

IV. Claims 33-39, drawn to reaction mixtures for producing polyketides, classified in class 435, subclass 183.

V. Claims 40-41, drawn to methods of making polyketides using reaction mixtures, classified in class 435, subclass 76.

VI. *Claims 44-50, drawn to* E. coli *host cells for producing methylmalonyl-CoA, classified in class 435, subclass 252.3.*

VII. *Claims 51-52, drawn to methods of making methylmalonyl-CoA, classified in class 435, subclass 88.*

3. New Group VI is related to Group I by virtue of the fact that both are drawn to host cells; these groups are related as combination (Group I) and subcombination (Group VI). Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (M.P.E.P. § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because the host cells of Group I need not produce methylmalonyl-CoA to produce polyketides (such as those using only malonyl-CoA as extender units). The subcombination has separate utility such as in the production of methylmalonyl-CoA for use in purposes other than the assembly of polyketides. The Examiner notes that Applicants' definition of a polyketide or a "complete" polyketide, which includes methylmalonyl-CoA as a polyketide (see specification, page 7), is found to be repugnant to the art (see 112 rejection below). A more reasonable, art definition of polyketide does *not* read on methylmalonyl-CoA.

New Group VII is not related to Group II for the same reasons as cited above for the distinctness of Groups VI and I. New Groups VI and VII are distinct for the same reasons previously cited for Groups I and II.

Election

4. Applicant's election without traverse of Group I in Paper No. 7 is acknowledged. Claims 10-23 and 30-41 have been cancelled.

Claims 1-9, 24-29, and 42-52 are pending in the instant application. Claims 44-52 are withdrawn from further consideration as non-elected inventions. Thus, Claims 1-9 and 24-29 will be examined herein.

Priority

5. The instant application is granted the benefit of priority for the U.S. Provisional Application Nos. 60/159,090 filed on October 13, 1999, 60/206,082 filed on May 18, 2000 and 60/232,379 filed on September 14, 2000 as requested in the declaration.

Information Disclosure Statement

6. The information disclosure statement filed on December 111, 2002 (Paper No. 5) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Objections to the Specification

7. The specification is objected to for lacking proper continuity data citation in the first paragraph. The instant application claims the benefit of particular applications, not merely "is related to" as cited in the first paragraph. Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

8. The specification is objected to for containing improper references to application numbers. On page 4, line 23, page 11, line 13, and page 17, line 18, two patented application numbers are referenced (09/346,860 and 08/989,332). These references must be updated to include the patent numbers 6,221,641 and 6,033,883, respectively. Moreover, numerous citations to applications still being prosecuted throughout the specification must be updated as their prosecution is completed.

9. In the specification, the title is objected to for not completely describing the claimed subject matter. Applicants must amend the title, depending on their amendments to the claims, to a host cell title more appropriate.

Claim Objections

10. Claim 9 is objected to for a typographical error. The word "spinosad" should be ---spinosyn---. In USPN 6,1435,26, the genes encoding the spinosyn PKS are taught. If "spinosad" is a typographical error in the claims, there is also a reference in the specification, which must be amended as well.

11. Claims 4-5 and 27 are objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Each of the instant claims limit their respective parent claims by use of the term "complete". As noted below, this term is unclear and, therefore, cannot further limit the subject matter clearly.

12. Claim 8 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The further limitation of the genetic modification is inconsistent with the limitations of the genetic modification in the parent claim, Claim 1. The expression of phosphopantetheinyltransferase neither produces a protein that produces a polyketide precursor nor disables an endogenous catabolic pathway.

13. Claim 9 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claim limits its parent claim by use of the term "derived from". As noted below, this term is unclear and, therefore, cannot further limit the subject matter clearly.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-9, 24-29, and 42-43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "polyketide" and "complete polyketide" are confusing. The specification uses terms such as "diketide", "triketide", "polyketide" and

"complete polyketide". On page 7, line 15, a definition of "complete polyketide" describes **any** antibiotic precursor including terms typically reserved for substrates, like methylmalonyl-CoA and malonyl-CoA, in the art. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). Particularly the further limiting nature of the word "complete" as its used in the claims renders the overall scope of the term "polyketide" confusing. Thus, the scope of the instant claims is unclear.

15. Claims 1-9 and 24-29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "starter unit" and "extender unit" are unclear in view of the broad and unclear definition of the term "polyketide" with respect to the art-defined vs. specification-defined definitions as noted above.

16. Claims 1-9, 24-29 (relating to *E. coli*), and 42-43 are rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See M.P.E.P. § 2172.01. The omitted elements are: an expression system for a phosphopantetheinyl transferase (ppt). The specification describes ppt as "essential" for the production of polyketides in non-native polyketide producers such as *E. coli*.

17. Claim 9 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The term "said at least one polyketide synthase protein" does not have proper antecedent basis in its parent Claims 1 or 4.

18. Claim 9 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "derived from" is unclear. The homology among PKS genes is very high, so much so that derivation might render a gene more similar to a PKS different from those listed in the instant claim. The scope of derivation is wholly unclear since no limit is noted.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 1-9, 24-29, and 42-43 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to prokaryotic, microbial, and/or *E. coli* host cells modified by genes which host cells are claimed *solely* by function and without any structural limitations.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject

matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material or host cell containing genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The genus of Claim 1 is broadly described in terms of functions: host cells modified for enhanced polyketide synthesis by (1) incorporation of an expression system for a protein that produces starter and/or extender units and/or (2) disabling an endogenous pathway of catabolism (breakdown) of starter and/or extender units. In the case of the first option, no real limitations on starter or extender units are clear. Therefore, expression systems for proteins that produce these products are virtually any enzyme producing a ketide-containing product. The instant specification describes the mat operon and the propionyl-CoA carboxylase subunits as useful genes in the claimed product. No correlation between structure and function is described. In the case of the second option, numerous pathways can be foreseen that involve catabolism of starter/extender units. The instant specification describes a single example of the prp operon in *E. coli*. No correlation between structure and function is described.

The instant claims are drawn to products claimed **solely** by virtue of their function with no limitation on their structure. No description of how the disclosed structures relate to the

claimed functions is offered. One of skill in the art would not be able to reasonably predict the structures of the genus based on the description in the specification.

Moreover, the Examiner notes that the breadth of the instant claims includes any polyketide synthase system. Firstly, one of skill in the art would not be able to reasonably predict the structures of the genus all possible PKS gene clusters based on the description in the specification. Moreover, it can be foreseen that some new PKS gene clusters might utilize different starter/extender units whose producing enzymes are wholly unknown with unknown functions and/or methods of disabling the catabolism of these starter/extender units are wholly unknown. The instant claims lack adequate written description for the full extent of their scope for the following:

the genus of proteins catalyzing the production of starter/extender units,

the genus of endogenous pathways for catabolism of starter/extender units,

the genus of phosphopantetheinyl transferases, and

the genus of polyketide synthase gene clusters.

20. Claims 1-9, 24-29, and 42-43 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for host cells comprising recombinant enzymes known to produce particular starter/extender units and/or known to have endogenous catabolic pathways for starter/extender units, does not reasonably provide enablement for host cells comprising **any** recombinant enzymes producing **any** starter/extender units and/or known to have **any** endogenous catabolic pathways for starter/extender units. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To

produce the claimed host cells according to the full scope of the claimed breadth would require undue experimentation on the part of one of skill in the art.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification provides particular working examples of host cells containing the *matABC* operon, containing the *pccB/accA2* genes, and/or having an inactivated *prp* operon. The specification presents no guidance or working examples for the identification of other analogous genes or operons to be used or disabled in the claimed host cells. The nature of the invention is such that a multitude of options are available to be used for the synthesis of

precursors and/or the disabling of catabolic pathways; however, all require an understanding of the polyketide synthase proposed for the host cells to be effective. The ability to predict which genes will be useful in which host cells for the production of which polyketides is very low considering all the possibilities of not only complete polyketides, such as erythromycin, but also analogs of complete polyketides and precursors or complete polyketides. Thus, the instant claims are not enabled to the full extent of their scope.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

21. Claims 1-3 are rejected under 35 U.S.C. § 102(a) as being anticipated by An *et al.* (A gene cluster encoding malonyl-CoA decarboxylase (MatA), malonyl-CoA synthetase (MatB) and a putative dicarboxylate carrier protein (MatC) in *Rhizobium trifolii*. Eur. J. Biochem. (1998 Oct. 15) 257:395-402). The instant claims are drawn to *E. coli* host cells that are genetically modified (for enhanced polyketide synthesis) wherein said modification is the incorporation of an expression system for a protein that produces a polyketide precursor (starter or extender unit).

An *et al.* teach the recombinant expression of the *Rhizobium trifolii matABC* cluster in *E. coli*; particularly, *matB* encodes malonyl-CoA synthetase for the production of malonyl-CoA. The expression taught by An *et al.* produces polyketide precursors in the *E. coli* host cells

rendering said host cells "genetically modified for enhanced" polyketide production. While the host cells taught by An *et al.* do not produce polyketides (*E. coli* natively do not produce polyketides), these cells do produce polyketide precursors, like malonyl-CoA, making said host cells "ready" for enhanced polyketide production meeting all the limitations of the instant claims.

22. Claims 1-3 are rejected under 35 U.S.C. § 102(a) as being anticipated by Rodriguez *et al.* (IDS reference 14). The instant claims are drawn to *E. coli* host cells that are genetically modified (for enhanced polyketide synthesis) wherein said modification is the incorporation of an expression system for a protein that produces a polyketide precursor (starter or extender unit).

Rodriquez *et al.* teach the recombinant expression of *Streptomyces coelicolor accA2* and *pccB* genes in *E. coli*. Said expression produces polyketide precursors in the *E. coli* host cells. Thus, these cells are not producing or being capable of producing large polyketides, like erythromycin, since they do not contain PKS genes; but these cells do produce polyketide precursors, like propionyl-CoA, which meets all the limitations of the instant claims.

Rodriquez *et al.* teach the recombinant expression of the *Streptomyces coelicolor accA2* and *pccB* genes in *E. coli*; particularly, *accA2* and *pccB* encode subunits of propionyl-CoA carboxylase for the production of methylmalonyl-CoA. The expression taught by Rodriquez *et al.* produces polyketide precursors in the *E. coli* host cells rendering said host cells "genetically modified for enhanced" polyketide production. While the host cells taught by Rodriquez *et al.* do not produce polyketides (*E. coli* natively do not produce polyketides), these cells do produce polyketide precursors, like methylmalonyl-CoA, making said host cells "ready" for enhanced polyketide production meeting all the limitations of the instant claims.

The Examiner also notes that, although the publication date of Rodriguez *et al.* is after the earliest priority date of the instant application, Rodriguez *et al.* clearly is prior to Applicants' invention as based on the discussion of Rodriguez *et al.* in the instant specification on page 6.

23. Claims 1-3 are rejected under 35 U.S.C. § 102(b) as being anticipated by Spratt *et al.* (Isolation and genetic characterization of *Escherichia coli* mutants defective in propionate metabolism. J Bacteriol (1981) 146(3):1166-9). The instant claims are drawn to *E. coli* host cells that are genetically modified (for enhanced polyketide synthesis) wherein said modification disables an endogenous pathway for propionate (a starter unit) metabolism.

Spratt *et al.* teach *E. coli* mutant defective in propionate metabolism. Said mutants were produced via chemical mutagenesis and are unable to grow on certain fatty acids indicating their inability to breakdown propionate. While the host cells taught by Spratt *et al.* do not produce polyketides (*E. coli* natively do not produce polyketides), these cells do have disabled propionate catabolism, making said host cells "ready" for enhanced polyketide production meeting all the limitations of the instant claims.

24. Claims 1-3 and 8 are rejected under 35 U.S.C. § 102(b) as being anticipated by Quadri *et al.* (IDS reference 13). The instant claims are drawn to *E. coli* host cells that are genetically modified (for enhanced polyketide synthesis) wherein said modification is the incorporation of at least one expression system for phosphopantetheinyl transferase. The Examiner notes that Claims 1-3 are included in the instant rejection because all the limitations of Claim 8 are met by Quadri *et al.*; however, the further limiting nature of Claim 8 is objected to above.

Quadri *et al.* teach the overexpression of *B. subtilis* ppt in *E. coli* (see page 1587, left column). While the host cells taught by Quadri *et al.* do not produce polyketides (*E. coli* natively do not produce polyketides), these cells do have the appropriate ppt expression, making said host cells "ready" for enhanced polyketide production meeting all the limitations of the instant claims.

25. Claims 1-2, 4, 6-7, 9, and 24-26 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kao *et al.* (IDS reference 9). The instant claims are drawn to *Streptomyces* host cells that are genetically modified to produce polyketides wherein without said modification, the host cells would not produce polyketides, wherein said modification is the incorporation of a gene encoding a protein that produces a polyketide precursor and wherein said host cells produce a polyketide using a PKS derived from erythromycin.

Kao *et al.* teach the expression of the complete DEBS PKS in a heterologous host cell, *Streptomyces coelicolor* CH999, which transformed host cell produces 6-dEB (see Abstract). CH999 does not produce polyketides in the absence of transformation. The DEBS expression system produces enzymes that catalyze the production of extender units. The DEBS expression system is derived from the erythromycin PKS.

26. Claims 1, 4, 9, and 24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Stassi *et al.* (IDS reference 15). The instant claims are drawn to microbial (prokaryotic) host cells (1) that have been modified to include a protein that produces a polyketide precursor and (2) that produce a polyketide using a PKS derived from erythromycin.

Stassi *et al.* teach *Saccharopolyspora* host cells that produce the polyketide 6-ethylErA, which is a derivative of erythromycin (see Abstract); the production of 6-ethylErA is catalyzed by the endogenous DEBS PKS whose AT domain (AT4) has been modified. Said host cells also recombinantly expressed crotonyl-CoA reductase for the production of butyryl-CoA, which is a precursor of the 6-ethylErA polyketide necessary for production in the host cell (see Abstract).

27. Claims 1, 2, 4, 9, and 24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Tang *et al.* (IDS reference 16). The instant claims are drawn to *Streptomyces* host cells (1) that have been modified to include a protein that produces a polyketide precursor and (2) that produce a polyketide using a PKS derived from spiramycin or tylosin.

Tang *et al.* teach *Streptomyces* host cells that produce the polyketides tylosin or spiramycin and that, in these host cells, "catabolism of valine is a major source of fatty acid precursors for macrolide biosynthesis" (see Abstract). Tang *et al.* also teach that valine dehydrogenase (vdh) is an enzyme responsible for valine catabolism and, thus, polyketide-precursor pools. Tang *et al.* teach the transformation of wild-type *Streptomyces* host cells with a *vdh* gene to increase the amount of valine catabolism which will increase the amount of macrolide production in the host cells (see Figure 4).

28. Claims 1-9, 24-29, and 42-43 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO98/27203 (Barr *et al.*) (IDS reference 2). The instant claims are drawn to *E. coli* host cells that are genetically modified and produce 6-dEB wherein without said modification, the host cells would not produce 6-dEB, wherein said modification is the incorporation of a gene encoding a protein that produces a polyketide precursor and/or a holo ACP synthase.

Barr *et al.* teach the co-expression of the 6-MSAS genes and the sfp gene in *E. coli* (see Example 2). *E. coli* do not natively produce 6-MSA; *E. coli* produce small amounts of 6-MSA with the inclusion of the 6-MSAS genes but in the absence of the sfp gene. Barr *et al.* also teach the co-expression of the DEBS genes and the sfp gene in *E. coli* (see Claims 1-3).

Conclusion

29. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

KMK
April 4, 2002